specification (37 CFR 1.78). The Examiner stated that this application does contain the required first sentence of the specification referencing the priority claim. The Examiner stated that however, it is noted that the reference does not clarify the filing date of PCT/US99/02289 as 3 February 1999. The Examiner stated that it is suggested that the specification be updated to include the cited date (i.e. page 1, line 7 - International Application No. PCT/US99/02289, filed February 3, 1998, which is a continuation-in-part of U.S. Serial No. 09/017,976, filed February 3, 1998."

In response, applicants have herein amended the specification such that the first paragraph references the filing date of PCT/US99/02289 as February 3, 1999. Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Drawings

The Examiner stated that the drawings in this application have been objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). The Examiner stated that applicant is required to submit a proposed drawing correction in reply to this Office action. The Examiner stated that however, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

In response, applicants will submit revised drawings upon the indication of allowable subject matter.

Oath or declaration

The Examiner stated that a new oath or declaration is required. The Examiner stated that the wording of an oath or declaration

cannot be amended. The Examiner stated that if the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The Examiner stated that the new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. The Examiner stated see MPEP §§ 602.01 and 602.02. The Examiner stated that the oath filed 12/01/99 and 2/28/00, list priority document No. 09/017,976 and PCT/US99/02289 with corresponding filing date as 3 February 1999. The Examiner stated that the correct filing date for Application No. 09/017,976 should be 3 February 1998. The Examiner stated that appropriate correction is required.

In response, applicants will prepare and file a revised declaration and power of attorney which lists the filing date of U.S. Serial No. 09/017,976 as February 3, 1998.

Specification

The Examiner stated that the abstract of the disclosure is objected to because of the following informalities. The Examiner stated that the first page of the specification should be numbered. The Examiner stated that applicants must supply a detailed description for Figure 7 which specifically identifies 7A and 7B. The Examiner stated that correction is required. The Examiner stated see MPEP §608.01(b).

In response, applicants first respectfully point out that the Examiner objected to the abstract of the disclosure and cited MPEP 608.1(b). However, applicants respectfully point out that the Examiner did not specifically address any problems with the

abstract. If the Examiner objects the any portion of the abstract, applicants request that the Examiner specifically point out such objection.

In addition, applicants have herein amended the specification such that the first page of the specification is numbered as page 1. Applicants have also amended the description for figure 7 such that it provides description for panels A and B.

Claim 69

The Examiner objected claim 69, stating that claim 69 step 2(vi) is mis-numbered and should be step (v). The Examiner stated that appropriate correction is required.

In response, applicants have herein amended claim 69 in accordance with the Examiner's suggestion. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

35 U.S.C. 112, second paragraph

The Examiner rejected claims 67-80 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claims 67, 68, 69, and 70 are vague and indefinite in utilizing the term "suitable" in suitable sample. The Examiner stated that it is not clear as to what limitation is being placed on the sample type. The Examiner stated that as recited the metes and bounds of the claim can not be determined. It is suggested that definite language replace "suitable" wherein

Applicants intended meaning can be clearly understood.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended the claims such that they recite the terms "urinary" and "blood" and not "suitable." Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

The Examiner stated that claims 67(ii), 68(ii), 69(ii), and 70(ii) recites the limitation "first portion and second portion" in "step 1". The Examiner stated that however, step 1 is directed to a suitable sample and does not distinctly refer to sample portions. The Examiner stated that there is sufficient antecedent basis for this limitation in the claim.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims such that there is sufficient antecedent basis for the terms "first portion" and "second portion" in the claims.

The Examiner stated that claims 67, 68, 69, and 70 have improper antecedent support in reciting "immobilizing capturing antibody". The Examiner stated that insert--a--before "capturing" for proper antecedent basis.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims such that there is

sufficient antecedent basis for the term "capturing antibody."

The Examiner stated that claims 67, 68, 69, and 70 are indefinite in reciting "any" in step (ii) because it is unclear what is encompassed by the term "any". The Examiner stated that deleting "any" and inserting--the- is suggested but not required so as to obviate indefiniteness and provide proper antecedent basis in the claims.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims such that they do not recite the term "any." Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated the phrase "continued high ratio" in claims 67(4), 68(4), and 70(4) employs the relative terms "continued" and "high" which are not defined by the claims. The Examiner stated that the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims such that they do not recite the term "continued high" with respect to ratio. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that in claims 71, 72, 73, and 74 the parenthetical symbols render the claims indefinite because it is unclear whether the limitation inside the parenthesis is part of the claimed invention.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended the claims such that the term "(hCG)" is no longer recited in the claims. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner stated that claims 72 and 74 are vague and indefinite in reciting step (C) because no such step was previously claimed.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended the claims 72 and 74 such that they no longer recite the term "step (c)" but instead recite the term "step (2)(b)." Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 71-74 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that the specification lacks complete deposit information for the deposit of hybridoma cell lines and monoclonal antibodies B108, B109, B152, and B207 in accordance with 37 CFR 1.801-1.809. The Examiner stated that while the specification provides enough information for one ordinary skill in the art to produce hybridoma cell lines and monoclonal antibodies with the same or similar properties of and monoclonal antibodies produced by the same (B108, B109, B152, and B207), reproduction of identical cell lines and antibodies is an extremely unpredictable event. The Examiner stated that because it does not appear that the monoclonal antibodies and their corresponding hybridoma cell lines, are known and publicly available or can be reproducibly isolated from nature without undue experimentation, a suitable deposit of the hybridoma cell lines and monoclonal antibodies for patent purposes is required.

The Examiner stated that if the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §§ 1.801-1.809, assurances regarding availability and permanency of deposits are required. The Examiner stated that such assurance may be in the form of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository required. The Examiner stated that the requirement is necessary when a deposit is made under the provisions of the Budapest Treaty

as the Treaty leaves this specific matter to the discretion of each State.

The Examiner stated that the amendment of the specification to recite the current practice requiring that a statement concerning all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this Application and that the deposit will be replaced if viable samples cannot be dispensed by the depository made in the instant Application. The Examiner stated that without such a statement, it would be impossible for the skilled artisan to practice the invention of claims 71-74 because the specific deposits cannot be placed into the hands of the artisan because other clones made from the source material have no predictable reasonable expectation of success of being identical to the single clone deposited.

The Examiner stated that furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. The Examiner stated that the declaration, executed by a person in a position to know should identify the deposited hybridomas and monoclonal antibodies by its depository accession number, establishes that the deposited hybridomas and monoclonal antibodies are the same as that described in the specification, and establish that the deposited hybridomas and monoclonal antibodies were in applicants' possession at the time of filing. The Examiner stated that applicant's attention is directed to In re Lundak, 773 F.2d.1216,27 USPQ 90 (CAFC 1985) and 37 CRF §§ 1.801-1.809 for further information concerning deposit practice.

In response, applicants have herein amended the specification to reflect the ATCC deposit information for the deposited hybridoma cell lines. A copy of the ATCC Deposit Receipt for B152 is attached hereto as Exhibit B. A copy of the ATCC Deposit Receipt for B109, B108 and B207 is attached hereto as Exhibit C. In addition, applicants will prepare a declarations with respect to a chain of custody for the hybridomas if deemed necessary. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

obviousness-type double patenting

The Examiner stated that claim 67-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53-81 of copending Application No. 09/017,976. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are not patentably distinct form the claims found in co-pending Application No. 09/017,976 because the claims employ the same method steps that encompass obvious modifications in assay design while utilizing the exact same reagents (i.e. molecular isoforms of hCG, non-nicked hCG, B152, B109, and B108). The Examiner stated that although one preamble recites "A method of predicting pregnancy outcome-09/017,976" and the other preamble recites "A method of detecting gestational trophoblast malignancy-09/311,428", the preambles are encompass the same subject matter and are not given patentable weight. In addition, the Examiner cited MPEP 2111.02 entitled. Weight of Preamble. The Examiner stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response, applicants respectfully traverse the Examiner's above rejection. Although the Examiner may not be according any patentable weight to the preamble, applicants point out that it is not merely the preamble which recites "gestational trophoblast malignancy." Applicants respectfully direct the Examiner's attention to step (4) of claims 67-70 which recites "wherein a determination of a continued high ratio indicates that the subject is afflicted with **gestational trophoblast malignancy**" [emphasis added]. Applicants point out that this is not recited in any portion of the claims in copending application U.S. Serial No. 09/017,976, which relates to predicting pregnancy outcome. The determination of gestational trophoblast malignancy is a not an obvious variation of the prediction of pregnancy outcome. Accordingly, an obviousness type double patenting rejection is not appropriate. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Provisional Rejection under 35 U.S.C. 103(a)

The Examiner provisionally rejected claims 67-80 under 35 U.S.C. 103(a) as being obvious over copending application No. 09/017,976 which has a common assignee with the instant application. The Examiner stated that based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if patented. The Examiner stated that this provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future patenting of the conflicting application. The Examiner stated that this provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by

another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. The Examiner stated that for applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. The Examiner stated see MPEP §706.02(1)(1) and § 706.02(1)(2). The Examiner stated that Please note: In the following rejections, the detection of gestational trophoblast malignancy is seen as intended use for methods detecting and evaluating non-nicked hCG and molecular isoforms of hCG in pregnancy/gestational diagnosis.

In response, applicants respectfully traverse the Examiner's above provisional rejection. Applicants will consider filing a declaration showing that the invention disclosed in the copending application is not by another.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 67-70, 73, 74, and 75-80 under 35 U.S.C. 103(a) as being unpatentable over Ellish et al. (Human Reproduction, 1996). The Examiner stated that Ellish et al. teach an immunoradiometric assay which has two solid-phase immobilized capture antibodies and one detection antibody to study early pregnancy loss. The Examiner stated that Ellish et al. employ B109 to capture non-nicked hCG molecule and B207 to capture free β core fragment. The Examiner stated that Ellish et al. utilized B108 as the radioactive labeled detection antibody. (Page 4074, column 2). The Examiner stated that although this reference does not specifically state that the assay will be repeated in order to determine continued high ratios as required in the repeating step (4) it is well known to those with ordinary skill in the art that

sampling at various points with multiple parameters is commonly used for in assay systems. The Examiner stated that methods for determining this data can be achieved by procedures known to those of ordinary skill in the art. The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art to repeat the sample analyses on samples sets and compare them to each other to evaluate the end results in the method demonstrated by Ellish et al. with a reasonable expectation of success and little additional labor because this information can be easily determined utilizing protocols/data points/etc. that are already being used in their methods, such as range sampling on various days of gestation (i.e. HCG concentrations on day 3, day 2-see Abstract). The Examiner stated that the repetition of samples in the method of Ellish et al. would have been an obvious modification to the existing method. The Examiner stated that one of ordinary skill in the art would utilize various comparative calculations for the resulting data sets to evaluated the particular diagnosis. The Examiner stated that these calculations are routine optimizations that are almost always determined and used in immunoassay studies. The Examiner stated that unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to repeat sample analysis on a given sample in the given method to determine the unknown diagnosis as a means of optimizing the assays provided by the art.

In response, applicants respectfully traverse the Examiner's above rejection. First, the Examiner asserts that the cited reference employs **B207** to capture free β subunit and hCG free β core fragment. Applicants respectfully disagree and point the Examiner's attention to page 407, second column which discloses the use of a **B204** antibody but not a B207 antibody. Second, applicants respectfully point out that the claimed invention relates to the

use of a **ratio** of the measurements of **two** molecules, i.e. an early pregnancy associated molecular isoform of hCG and an intact non-nicked isofom of hCG. Nothing in the cited reference discloses a determination of a ratio by measuring the amounts of any two molecules, let alone the two molecules recited in applicants' claimed invention, i.e. early pregnancy associated molecular isoform of hCG and intact non-nicked hCG. Moreover, the claims relate to a detection of **gestational trophoblast malignancy**. In contrast, the cited reference describes early pregnancy loss but does not suggest that any measurements, let alone a ratio of two molecules, could be used to detect gestational trophoblast malignancy. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground if rejection.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 67-70, 72, 74, and 75-80 under 35 U.S.C. 103(a) as being unpatentable over Birken et al. (Endocrinology 1993). The Examiner stated that Birken et al. disclose a two-site immunoradiometric assay to evaluate immunopotency of nicked hCG. The Examiner stated that Birken et al. further teach a capture antibody that specifically binds non-nicked hCG(intact hCG heterodimer) along with a detecting (tracer) antibody. The Examiner stated that the capture antibody is B109 and the I125 radiolabeling antibody is B108. (See page 1391, column 1). The Examiner stated that although this reference does not specifically state that the assay will be repeated in order to determine continued high ratios as required in the repeating step (4) it is well known to those with ordinary skill in the art that sampling at various points with multiple parameters is commonly used in assay systems. The Examiner stated that methods for determining this data can be achieved by procedures known to those

of ordinary skill in the art. The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art to repeat the sample analyses on sample sets and compare them to each other to evaluate the end results in the method demonstrated by Birken et al. with a reasonable expectation of success and little additional labor because this information can be easily determined utilizing protocols/data points/etc. that are already being used in the cited method. The Examiner stated that the repetition of samples in the method of Birken et al. would have been an obvious modification to the existing method. The Examiner stated that one of ordinary skill in the art would utilize various comparative calculations for the resulting data sets to evaluate the particular diagnosis. The Examiner stated that these calculations are routine optimizations that are almost always determined and used in immunoassay studies. The Examiner stated that unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to repeat sample analysis on a given sample in the given method to determine the unknown diagnosis as a means of optimizing the assays provided by the art.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point out that the claimed invention relates to the use of a **ratio** between an early pregnancy associated molecular isoform of hCG and an intact non-nicked isofom of hCG. Nothing in the cited reference discloses the measurement of **two** molecules to determine a **ratio**, wherein the ratio is then used for a prediction. In contrast, the cited reference relates to the measurement of only one molecule in the immunoassay, as described on page 1391, first column under the heading "Immunoassay." The cited reference discloses an assay using either B109 or B210 capturing antibody and B108 detecting antibody. There is no

suggestion of determining a ratio of different antibodies and thus, no suggestion of determining a ratio of different analytes. In fact, such would not be possible in the assay disclosed in the cited reference since there is only one detecting antibody and therefore, one would not be able to distinguish between two different molecules. At most, from the disclosure of the cited reference, one may have been motivated to repeat the measurement for a single molecule. However, there is no suggestion to take any ratio, let alone multiple ratio measurements. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground if rejection.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 67-70, 72, 74, and 75-80 under 35 U.S.C. 103(a) as being unpatentable over by O'Connor et al. (Cancer Research, 1988). The Examiner stated that O'Connor et al. disclosed assays to evaluate hCG function. The Examiner stated that O'Connor et al. specifically teach immobilized capture antibodies via B108 or B109 coated solid phase materials which specifically bind non-nicked hCG. (See page 1362, column 1). The Examiner stated that although this reference does not specifically state that the assay will be repeated in order to determine continued high ratios as required in the repeating step (4) it is well known to those with ordinary skill in the art that sampling at various points with multiple parameters is commonly used for in assay systems. The Examiner stated that methods for determining this data can be achieved by procedures know to those or ordinary skill in the art. The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art to repeat the sample analyses on sample sets and compare them to each other to evaluate the end results in the method demonstrated by O'Connor et al. with a reasonable expectation of success and little additional labor

because this information can be easily determined utilizing protocols/data points/etc. that are already being used in their methods, such as range sampling to determine Inter-and Intra-assay variation (1362-Quality Control Evaluation of Immunoassay). The Examiner stated that the repetition of samples in the method of O'Connor et al. would have been an obvious modification to the existing method. The Examiner stated that one of ordinary skill in the art would utilize various comparative calculations for the resulting data sets to evaluated the particular diagnosis. The Examiner state that these calculations are routine optimizations that are almost always determined and used in immunoassay studies. The Examiner stated that unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to repeat sample analysis on a given sample in the given method to determine the unknown diagnosis as a means of optimizing the assays provided by the art.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point out that the claimed invention relates to the use of a **ratio** between an early pregnancy associated molecular isoform of hCG and an intact non-nicked isofom of hCG. Nothing in the cited reference discloses the measurement of **two** molecules to determine a ratio which ratio is then used to for a prediction. In contrast, the cited reference relates to the measurement of only one molecule in the immunoassay, as described on page 1362, first column. The cited reference discloses an assay using either B109 or B204 capturing antibody and B108 detecting antibody. There is no suggestion of determining a ratio of different antibodies. In fact, such would not be possible in the assay disclosed in the cited reference since there is only one detecting antibody and therefore, one would not be able to distinguish between two different molecules. At most, from the

disclosure of the cited reference, one may have been motivated to repeat the measurement for a single molecule. However, there is no suggestion to take any ratio, let alone multiple ratio measurements. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Allowable Subject Matter

Applicants acknowledge the Examiner's statement that claim 71 is free of the prior art of record which neither teach or suggest the instant molecular isoform of hCG or a characteristic epitope thereof defined by the specific binding of monoclonal antibody B152. The Examiner stated that claim 71 is objected to as being dependant upon a rejected base claim but it would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In response, applicants contend that in view of the arguments above, claims 67-70 are allowable and therefore, claim 71 is not dependant on a rejected base claim and is allowable.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 67-80.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone either of them at the number provided below.

No fee, other than the enclosed $445.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

7-17-01

John P. White Date
Reg. No. 28,678
Spencer H. Schneider
Reg. No. 45,923

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Exhibit A

--67.(Amended) A method for detecting gestational trophoblast malignancy in a subject which comprises:

(1) collecting a [suitable] urinary or blood sample from the subject and separating the sample into a first portion and a second portion;

(2) performing the following steps (a) and (b) which may be performed in any order:

(a) (i) immobilizing capturing antibody on a solid matrix under conditions permitting binding of the capturing antibody to the solid matrix, wherein the capturing antibody specifically binds to an early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)];

(ii) contacting the immobilized capturing antibody with [a] the first portion of the sample obtained in step (1) under conditions permitting binding of the capturing antibody to [any] the early pregnancy associated molecular isoform of [hCG] human chorionic gonadotropin present in the sample so as to form a complex;

(iii) removing [any] unbound sample from the complex;

(iv) contacting the complex with a detecting antibody which specifically binds to an early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)], under conditions permitting binding of the detecting antibody to the

[hCG] human chorionic gonadotropin so as to form a complex;

(v) removing [any] unbound detecting antibody;

(vi) determining the amount of detecting antibody which binds to the complex;

(b) (i) immobilizing a capturing antibody on a solid matrix under conditions permitting binding of the capturing antibody to the solid matrix, wherein the capturing antibody specifically binds to intact non-nicked human chorionic gonadotropin [(hCG)];

(ii) contacting the immobilized capturing antibody with [a] the second portion of the sample obtained in step (1) under conditions permitting binding of the capturing antibody to [any] the intact non-nicked human chorionic gonadotropin [(hCG)] present in the sample so as to form a complex;

(iii) removing [any] unbound sample from the complex;

(iv) contacting the complex with detecting antibody which specifically binds to intact non-nicked human chorionic gonadotropin [(hCG)] under conditions permitting binding of the detecting antibody to the [hCG] human chorionic gonadotropin so as to form a complex;

(v) removing [any] unbound detecting antibody;

(vi) determining the amount of detecting antibody which binds to the complex;

(3) comparing the amount of antibody measured in step (2)(a) with the amount of antibody measured in step (2)(b), so as to thereby determine a ratio of the amount of antibody measured in step (2)(a) with the amount of antibody measured in step (2)(b);

(4) repeating steps (2) through (3) throughout the apparent pregnancy to determine a profile of the ratios, wherein a [continued high] profile of ratios which do not diminish and are greater than 1.0 indicates that the subject is afflicted with gestational trophoblast malignancy.--

--68.(Amended) A method for detecting gestational trophoblast malignancy in a subject which comprises:

(1) collecting a [suitable] urinary or blood sample from the subject and separating the sample into a first portion and a second portion;

(2) performing the following steps (a) and (b) which may be performed in any order:

(a) (i) immobilizing a capturing antibody on a solid matrix under conditions permitting binding of the capturing antibody to the solid matrix, wherein the capturing antibody specifically binds to an early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)];

(ii) contacting the immobilized capturing antibody with [a] the first portion of the sample obtained in step (1) under conditions permitting binding of the capturing antibody to [any] the early

pregnancy associated molecular isoform of [hCG] human chorionic gonadotropin present in the sample so as to form a complex;

(iii) removing [any] unbound sample from the complex;

(iv) determining the amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] which is bound to the capturing antibody in the complex;

(b) (i) immobilizing a capturing antibody on a solid matrix under conditions permitting binding of the capturing antibody to the solid matrix, wherein the capturing antibody specifically binds to intact non-nicked human chorionic gonadotropin [(hCG)];

(ii) contacting the immobilized capturing antibody with [a] the second portion of the sample obtained in step (1) under conditions permitting binding of the capturing antibody to [any] the intact non-nicked human chorionic gonadotropin [(hCG)] present in the sample so as to form a complex;

(iii) removing [any] unbound sample from the complex;

(iv) determining the amount of intact non-nicked human chorionic gonadotropin [(hCG)] which is bound to the capturing antibody in the complex;

(3) comparing the amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] measured in step (2)(a) with the amount of intact non-nicked human chorionic gonadotropin [(hCG)] measured in step (2)(b), so as to thereby determine a ratio of the amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] measured in step (2)(a) measured in step (2)(a) with the amount of intact non-nicked human chorionic gonadotropin [(hCG)] measured in step (2)(b);

(4) repeating steps (2) through (3) throughout the apparent pregnancy to determine a profile of the ratios, wherein a [continued high] profile of ratios which do not diminish and are greater than 1.0 indicates that the subject is afflicted with gestational trophoblast malignancy.--

--69.(Amended) A method for detecting gestational trophoblast malignancy in a subject which comprises:

(1) collecting a [suitable] urinary or blood sample from the subject and separating the sample into a first portion and a second portion;

(2) performing the following steps (a) and (b) which may be performed in any order:

(a) (i) contacting [one] the first portion of the sample obtained in step (1) with a capturing antibody which binds to an early pregnancy associated molecular isoform of human chorionic gonadotropin under conditions permitting binding of the capturing antibody to [any] the early pregnancy associated molecular isoform of hCG present in the sample so as to form a

complex;

(ii) removing [any] unbound sample and [any] unbound capturing antibody from the complex;

(iii) contacting the complex with a detecting antibody which specifically binds to an early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)], under conditions permitting binding of the detecting antibody to the [hCG] human chorionic gonadotropin so as to form a complex;

(iv) removing [any] unbound detecting antibody;

[(vi)] (v) determining the amount of detecting antibody which binds to the complex;

(b) (i) contacting [a] the second portion of the sample obtained in step (1) with a capturing antibody which binds to intact non-nicked human chorionic gonadotropin under conditions permitting binding of the capturing antibody to [any] the intact non-nicked human chorionic gonadotropin [(hCG)] present in the sample so as to form a complex;

(ii) removing [any] unbound sample and [any] unbound capturing antibody from the complex;

(iii) contacting the complex with a detecting antibody which specifically binds to intact non-nicked human chorionic gonadotropin [(hCG)] under conditions

permitting binding of the detecting antibody to the [hCG] human chorionic gonadotropin so as to form a complex;

(iv) removing [any] unbound detecting antibody;

(v) determining the amount of detecting antibody which binds to the complex;

(3) comparing the amount of antibody measured in step (2)(a) with the amount of antibody measured in step (2)(b), so as to thereby determine a ratio of the amount of antibody measured in step (2)(a) with the amount of antibody measured in step (2)(b);

(4) repeating steps (2) through (3) throughout the apparent pregnancy to determine a profile of the ratios, wherein a [continued high] profile of ratios which do not diminish and are greater than 1.0 indicates that the subject is afflicted with gestational trophoblast malignancy.--

--70.(Amended) A method for detecting gestational trophoblast malignancy in a subject which comprises:

(1) collecting a [suitable] urinary or blood sample from the subject and separating the sample into a first portion and a second portion;

(2) performing the following steps (a) and (b) which may be performed in any order:

(a) (i) contacting [one] the first portion of the sample obtained in step (1) with a capturing antibody which binds to an early pregnancy associated molecular isoform ofhuman chorionic gonadotropin under conditions permitting binding of the capturing antibody to [any] the early

pregnancy associated molecular isoform of [hCG] human chorionic gonadotropin present in the sample so as to form a complex;

(ii) removing [any] unbound sample and [any] unbound capturing antibody from the complex;

(iii) determining the amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] which is bound to the capturing antibody in the complex;

(b) (i) contacting [a] the second portion of the sample obtained in step (1) with a capturing antibody an intact non-nicked human chorionic gonadotropin under conditions permitting binding of the capturing antibody to [any] the intact non-nicked human chorionic gonadotropin [(hCG)] present in the sample so as to form a complex;

(ii) removing [any] unbound sample and [any] unbound capturing antibody from the complex;

(iii) determining the amount of intact non-nicked human chorionic gonadotropin [(hCG)] which is bound to the capturing antibody in the complex;

(3) comparing the amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] measured in step (2)(a) with the amount of intact non-nicked human chorionic gonadotropin [(hCG)] measured in step (2)(b), so as to thereby determine a ratio of the

amount of early pregnancy associated molecular isoform of human chorionic gonadotropin [(hCG)] measured in step (2)(a) measured in step (2)(a) with the amount of intact non-nicked human chorionic gonadotropin [(hCG)] measured in step (2)(b);

(4) repeating steps (2) through (3) throughout the apparent pregnancy to determine a profile of the ratios, wherein a [continued high] profile of ratios which do not diminish and are greater than 1.0 indicates that the subject is afflicted with gestational trophoblast malignancy.--

--71. (Amended) The method of any one of claims 67-70, wherein the capturing antibody of step (2)(b) is B152 (ATCC Designation No. HB-12467).--

--72. (Amended) The method of any one of claims 67-70, wherein the capturing antibody of step [(c)] (2)(a) is B109 is (ATCC Designation No. PTA-1624).--

--73. (Amended) The method of claim 67 or 69, wherein the detecting antibody of step (2)(b) is B207 (ATCC Designation No. PTA-1626).--

--74. (Amended) The method of claim 67 or 69, wherein the detecting antibody of step [(c)] (2)(a) is B108 (ATCC Designation No. PTA-1625).--

American Type Culture Collection

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

T : (Name and Address of Depositor or Attorney)

Cooper & Dunham LLP
Attn: John P. White, Esq.
1185 Avenue of the Americas
New York, NY 10036

Dep sited on Behalf of: The Trustees of Columbia University in the City of New York
(Ref. Docket 54205/JPW/SBS)

Identification Reference by Depositor:	**ATCC Designation**
Mouse hybridoma B152	HB-12467

The deposit was accompanied by: __ a scientific description _a proposed taxonomic description indicated above.

The deposit was received February 3, 1998 by this International Depository Authority and has been accept d.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right t receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested February 20, 1998. On that date, the culture was viable.

Int rnational Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: February 23, 1998

cc: **Steven B. Stein**

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

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To: (Name and Address of Depositor or Attorney)

Cooper & Dunham LLP
Attn: John P. White, Esq.
1185 Avenue of the Americas
New York, NY 10036

Deposited on Behalf of: The Trustees of Columbia University in the City of New York

Identification Reference by Depositor:	**Patent Deposit Designation**
Mouse hybridoma cell line: B109 4D5	PTA-1624
Mouse hybridoma cell line: B108	PTA-1625
Mouse hybridoma cell line: B207	PTA-1626

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received April 4, 2000 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested April 18, 2000. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara E. Coupé

Barbara E. Coupé, Administrator, Patent Depository

Date: April 27, 2000

cc: